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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,605	GOLEMBO ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-59 and 67-96* is/are pending in the application.

4a) Of the above claim(s) *34,35,45-59 and 67-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-33 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *19 March 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 31-44 in the reply filed on 9 January 2006 is acknowledged. In addition, Applicants elect the species of SEQ ID NO: 5. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 34 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, SEQ ID NOs: 1-4, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9 January 2006. Claim 45 is amended and claims 67-96 are new. Claims 45 and 67-96 are withdrawn from consideration as being drawn to non-elected methods of treatment. Claims 31-33 and 36-44 are pending and under examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because the residence and city is missing.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Israel on 20 March 2001. It is noted, however, that applicant has not filed a certified copy of the 00142118 application as required by 35 U.S.C. 119(b), thus the requirement for obtaining benefit of the earlier filed application has not been met.

Sequence Rules

The specification is not in compliance with sequence rules. The sequences listed on p. 24 must have SEQ ID NOs associated with them. Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: The description of Figure 4 does not provide all the details of the Figure, for instance, what B, Xa and H represent. Appropriate clarification is required.

Drawings

The drawings are objected to because Figures 3A-3C because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures

appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 43-44 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not further limit the ***composition*** of their parent claims, but rather, only the ***intended use*** of the composition.

With regard to claim 31, and the claims that depend from it, please note that the phrase "for bone elongation" is an intended use phrase. A statement of the purpose or

intended use of the invention is not considered a limitation on claim construction, and is given little patentable weight for the purpose of prior art.

Claim Rejections - 35 USC § 112

Claims 31-32, 36-38 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising CNP variants according to SEQ ID NO: 5 (including SEQ ID NOs: 10, 45-47, 54-60 and 65-69) does not reasonably provide enablement for at least one natriuretic peptide or CNP or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims reciting at least one natriuretic peptide or CNP or variants thereof amount to single means claims. Single means claims are those that cover every

conceivable means for achieving the stated purpose. Single means claims are nonenabling for the scope of the claim because the specification discloses at most only those means known to the inventor, in this case, CNP variants of SEQ ID NO: 5. When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See MPEP 2164.08(a).

In addition, the nature of administration of proteins as pharmaceutical compositions is complex. Proteins have short half-lives and are quickly metabolized in vivo. Furthermore, according to p. 21, Table 3 of the Specification, Applicant has listed numerous 17mer variants of CNP that vary greatly in their relative binding capabilities, thus presumably, not all pharmaceutical compositions would perform equally well. In fact, p. 22, lines 7-10 contain an admission that variants with the substitution of Phe at residue 7 (including SEQ ID NOs: 24-25, 27-34 and 69-71) resulted in reduced activity.

Due to the large quantity of experimentation necessary to determine which natriuretic peptide variants achieve bone elongation when administered as a pharmaceutical composition, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of amino acid substitutions on function (see p. 21-22 of the Specification), and the breadth of the claims which fail to recite limitations on the function of the CNP to be used in the

pharmaceutical composition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In addition, claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, because the specification does not reasonably provide enablement for a pharmaceutical composition comprising a CNP and an inhibitor of tyrosine kinase for the purpose of treating skeletal dysplasias. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention is complex. The literature is silent with respect to the therapeutic use of tyrosine kinases for the treatment of skeletal dysplasias. In the absence of examples in the literature, the specification should provide some guidance

with respect to the treatment of skeletal dysplasias with tyrosine kinase inhibitors. However, the specification does not provide any guidance or working examples to demonstrate that this embodiment of the invention is enabled. Tyrosine kinases are used in the treatment of cancer. For a review of selected tyrosine kinase inhibitors on the market see, Druker and Lydon, J Clin Invest. 2000; 105: 3-7; especially, p. 3 Table 1. Because the literature is silent with respect to the treatment of skeletal dysplasias with tyrosine kinase inhibitors, the predictability in the art is necessarily low. Even in cases where a nexus has been established between a specific disease and an alteration in levels of a particular protein, as the specification points out with respect to skeletal dysplasias and FGFR (see for example, p. 6, lines 5-11), it cannot be predicted whether or not an effective medication can be made based on that information alone. The skilled artisan cannot predict whether or not a new drug will be effective without empirical testing. Because of the low predictability in the art, the quantity of experimentation required to practice the invention would be very large, considering that tyrosine kinase inhibitors must be screened (including dosage, administration routes, contraindications, endpoint determination) and decided empirically.

Due to the large quantity of experimentation necessary to determine if tyrosine kinase inhibitors would be effective in the treatment of skeletal dysplasias, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention and the unpredictability in the art with respect to the treatment of skeletal dysplasias with

tyrosine kinase inhibitors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32 and 43-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanaka et al. (Patent No. 5,434,133—citation A6 on Applicants' 1449 form). Tanaka et al. teach at column 12, lines 19-45 and column 13, lines 18-37, a pharmaceutical composition comprising a CNP or variants thereof. Note that that the phrase "for bone elongation" is an intended use phrase. A statement of the purpose or intended use of the invention is not considered a limitation on claim construction, and is given little patentable weight for the purpose of prior art.

In addition, claim Claims 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. (FEBS Letters, 1991; 282: 321-325). Suzuki et al. teach a CNP variant isolated from dogfish, that encompasses SEQ ID NO: 5, and shares sequence homology with porcine and rat CNP at the C-terminus (see p. 324, Figure 4, and p. 323, left column, under Discussion). According to Suzuki et al., it is well accepted that mature CNP peptides are cleaved from the C-terminal ends of

prohormones. Furthermore, the 17 amino acid C terminus, which corresponds to SEQ ID NO: 5, is a ring-structure with a disulfinde bond and is common to natriuretic peptides. Finally, Suzuki et al. suggest at p. 323, right column, last paragraph, that their data suggest the high homology between dogfish and mammals of the C-terminal segment suggest that this region of CNP has an important biological role in vertebrates.

In addition, claims 31 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohbayashi et al. (citation C15 on Applicants' 1449 form). Ohbayashi et al. teach co-admininstration of thiorphan with administration of CNP in order to potentiate the effects of CNP (see abstract and p. 987, right column, 2nd paragraph under Drugs and chemicals).

Finally, claims 31, 40 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Yabuta (EP 0 528686 A2, published 24 February 1993). Yabuta teach a fusion protein consisting of a CNP variant (the target peptide) fused to a protective peptide, wherein a linker peptide is positioned between the C-terminal of the protective peptide and the N-terminal of CNP.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuta as applied to claims 31 and 40 above (under **Rejections under 35 USC 102**), and further in view of Rivera et al. (Science 2000; 287: 826-830) and Mericq et al. (J Clin Endocrinol Metab. 2000; 85: 569-73). As state above, Yabuta teach a fusion protein consisting of a CNP variant (the target peptide) fused to a carrier protein. Yabuta does not teach that the CNP variant is attached to growth hormone (GH). Rivera et al. teach that GH can be fused to another human protein (see. p. 827, Figure 1) to promote storage in the endoplasmic reticulum (ER). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Yabuta by fusing CNP to the modified GH carrier peptide described in Rivera because the authors demonstrate that the fusion protein can be stored in the ER thus potentially enabling controlled release of therapeutic proteins (see p. 829, right column, 1st paragraph) and presumably eliminating the need for frequent injections in

protein therapy. There was a need in the art for this because it was generally accepted that protein administration requires frequent and uncomfortable injections. Furthermore, the artisan of ordinary skill would have been motivated to fuse CNP and GH because, as is underscored by Mericq et al., GH was used to treat GH deficiency in children with short stature (see p. 569, left column first paragraph), thus GH was recognized in the art as therapy for bone elongation. Furthermore, the ordinarily skilled practitioner could reasonably have expected success because Yabuta describe the successful manufacture of the fusion protein (see p. 13-14, Examples 7-8) and claim that their invention avoids the rapid degradation which occurs when proteins are produced recombinantly (p. 2, lines 3-13) and because therapy with GH for the treatment of short stature was well established in the art. Thus the claims do not contribute anything non-obvious over the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER